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(54) Title: PH RESPONSIVE BIODEGRADABLE POLYLACTIC ACID DERIVATIVES FORMING POLYMERIC MICELLES AND USES THEREOF FOR POORLY WATER SOLUBLE DRUG DELIVERY

(57) Abstract: Polylactic acid derivatives capable of forming micelles in an aqueous solution with a pH of 4 or above, having one terminal carboxyl group. The polylactic acid derivatives may be applied as a drug delivery system in various forms since poorly water soluble drugs can be entrapped inside the micelles.

CLAIMS

We claim:

1. A polylactic acid derivative capable of forming micelles in an aqueous solution with a pH of 4 or more, said polylactic acid derivative can be represented by formula (I):



wherein A is -COO-CHZ; B is -COO-CHY-, -COO-CH₂CH₂CH₂CH₂CH₂-, or -COO-CH₂CH₂OCH₂-; R is hydrogen, an acetyl, benzoyl, decanoyl, palmitoyl, methyl, or ethyl group; Z and Y are hydrogen, methyl, or phenyl groups; M is hydrogen, sodium, potassium, or lithium; n is an integer from 1 to 30; and m is an integer from 0 to 20.

2. The polylactic acid derivative according to claim 1 wherein the number average molecular weight of the polylactic acid derivative is 500 to 2,000 Daltons.

- 15 3. The polylactic acid derivative according to claim 1 wherein the polylactic acid derivative is a member selected from the group consisting of D,L-polylactic acid, a copolymer of D,L-lactic acid and mandelic acid, a copolymer of D,L-lactic acid and glycolic acid, a copolymer of D,L-lactic acid and caprolactone, and a copolymer of D,L-lactic acid and 1,4-dioxane-2-one.

4. The polylactic acid derivative according to claim 1 wherein M is sodium, potassium, or lithium.

5. The polylactic acid derivative according to claim 1 wherein R is decanoyl or
25 palmitoyl.

6. A polylactic acid derivative, made from a process comprising:

 - 1) polycondensing monomers of a polylactic acid derivative at an elevated temperature under a reduced pressure;
 - 2) adding distilled water to the product of step 1 to precipitate the polylactic acid

- derivative and thereby removing a low-molecular weight oligomer;
- 3) adding the polylactic acid derivative to a neutral or alkaline aqueous solution to dissolve the polylactic acid derivative;
- 4) isolating the polylactic acid derivative from the solution of step 3; and
- 5) adding an alkali metal salt to the polylactic acid derivative obtained in step 4.
7. The polylactic acid derivative according to claim 6 wherein the reaction temperature of the polycondensation in step 1 is 100 to 200 °C.
- 10 8. The polylactic acid derivative according to claim 6 wherein the polycondensation in step 1 is conducted under a pressure of 25 to 0.1 mmHg.
9. The polylactic acid derivative according to claim 6 wherein isolating the polylactic acid derivatives in step 4 is conducted by adding acid to the aqueous solution of step 15 3 and adjusting pH to 1.5 ~ 2.5 to precipitate the polylactic acid derivatives.
10. The polylactic acid derivative according to claim 6 wherein isolation of the polylactic acid derivative in step 4 is conducted by adding an organic solvent to the aqueous solution of step 3 to extract the polylactic acid derivative.
- 20 11. The polylactic acid derivative according to claim 6 wherein the alkali metal salt in step 5 is selected from the group consisting of sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate and lithium carbonate.
- 25 12. A polylactic acid derivative of formula (I) wherein R is an acetyl, benzoyl, decanoyl, palmitoyl, methyl, or ethyl group, prepared from a process comprising the steps of:
- 1) polycondensing a monomer of a polylactic acid derivative at an elevated temperature and under a reduced pressure;
- 2) adding distilled water to the product of step 1 to a precipitate a polylactic acid derivative and thereby removing low-molecular weight oligomers;

- 3) adding the polylactic acid derivative to a neutral or alkaline aqueous solution to dissolve the polylactic acid derivative;
 - 4) isolating the polylactic acid derivative from the solution of step 3;
 - 5) reacting the polylactic acid derivative obtained in step 4 with acetic anhydride, acetyl chloride, benzoyl chloride, decanoyl chloride, palmitoyl chloride, methyl iodide, or ethyl iodide to substitute the hydroxyl terminal group; and
 - 6) adding an alkali metal salt to the substituted polylactic acid derivatives.
13. The polylactic acid derivative according to the claim 12 wherein the reaction temperature of the polycondensation in step 1 is 100 to 200°C.
14. The polylactic acid derivative according to the claim 12 wherein the polycondensation in step 1 is conducted under a pressure of 25 to 0.1 mmHg.
15. 15. The polylactic acid derivative according to the claim 12 wherein the step of isolating the polylactic acid derivative in step 4 is conducted by adding acid to the aqueous solution of step 3 and adjusting pH to 1.5 ~ 2.5 to precipitate the polylactic acid derivative.
- 20 16. The polylactic acid derivative according to the claim 12 wherein the step of isolating the polylactic acid derivative in step 4 is conducted by adding an organic solvent to the aqueous solution of step 3 to extract the polylactic acid derivative.
- 25 17. The polylactic acid derivative according to the claim 12 wherein the alkali metal salt in step 5 is selected from the group consisting of sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, and lithium carbonate.
18. A polymeric composition containing the polymeric micelles comprising the polylactic acid derivative according to any one of the claims 1 to 17.

19. A pharmaceutical composition wherein a poorly water soluble drug is entrapped in the polymeric micelles comprising the polylactic acid derivative according to any one of the claims 1 to 17.